In the latest report from the United Kingdom Childhood Cancer Study (UKCCS), Roman et al. (1) describe an association between early-onset childhood acute lymphoblastic leukemia (ALL) and increased early infections. This study is a welcome development, following the studies that used proxy measures for infectious exposure (2). Roman et al. concede that the results do not support Greaves’ delayed infection hypothesis (3) but conclude that they point towards an abnormal immune response to infection (1). We believe there may be alternative explanations.

One hypothesis the UKCCS was launched to test was that the development of ALL is related to “abnormal responses to common infectious agents” triggered by “paucity of infectious exposure in infancy” (4, p. 1074). Many studies, including another UKCCS study (5), have seemed to support a pattern of reduced exposure to infections preceding the development of childhood leukemia. Roman et al. (1) directly investigated observed episodes of infection, and the results are inconsistent with previous studies. They conclude that their findings “support the hypothesis that a dysregulated immune response to infection in the first few months of life promotes transition to overt ALL” (1, p. 496). However, the original hypothesis predicted an abnormal response by an immune system that remained immature due to lack of infectious exposures early in life; the hypothesis has been reiterated more recently (6).

Abnormal immune response has been speculated about but not observed in childhood ALL. Data generated from studies using proxy measures for exposure or observations of population mixing and space-time clustering (2, 6, 7) have valid alternative explanations. In support of an abnormal immune response, now purported to be triggered by a surfeit rather than a deficit of early infections, Roman et al. cite another UKCCS study (8). That association study investigated the immunologically least functional human leukocyte antigen (HLA) locus DPB1 but not the other loci involved in human and animal leukemias. Any interpretation of single-locus HLA association studies is difficult because of confounding by locus. The cited study found no age-specific difference in DPB1 frequencies (8). It is unclear how the statistical association provides evidence for a relation between infections and early-onset ALL. Both UKCCS studies used the same sample, and the data should be available for correlation of the HLA-DPB1 genotype with infection frequencies.

There may not be any consequential relation between infections and leukemia. Frequent infection suggests a less functional immune system. Such children will be at high cancer risk because of the parallels between immune response to infectious agents and neoplastic transformations. In recent research, Dunn et al. (9) and Kinlen (10) concluded that immune surveillance is relevant for any cancer, not just for virus-induced ones as previously thought. The model of immune impairment and increased cancer risk is supported by a replicated homozygous HLA-DR region association with childhood ALL (11, 12), which is more relevant because of the recessive nature of immune nonresponsiveness and because it is most similar to the H-2 association in homozygous mice (13, 14). Another related model has also been presented (15). Some of the frequent infections in infancy are caused by viruses that establish persistent infections in lymphoid cells. In particular, adenoviruses show the greatest known molecular mimicry with the HLA-DR53 molecule—the risk marker for childhood ALL—and persist in precursor B lymphocytes using their immunoevasive properties (15). These properties hide infected lymphoid cells from immune surveillance and will also help promote a transformed precursor B lymphocyte to overt leukemia. Given the sex bias in both childhood ALL (16) and childhood infections (17), particularly in infancy (18), the observed association should be stronger among boys (as is the HLA-DR association (11, 12)). However, results of sex-specific analyses were not presented by Roman et al. (1).

These alternative explanations of the UKCCS data should also be considered. Instead of invoking an abnormal immune response, we favor the explanation that subtle immunodeficiency results in increased infections as well as increased ALL risk.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCES


M. Tevfik Dorak1,2, Richard J. Q. McNally1, and Louise Parker3 (e-mail: dorakmt@dorak.info)

1 Sir James Spence Institute of Child Health, School of Clinical Medical Sciences, Faculty of Medical Sciences, Newcastle University, Newcastle NE1 4LP, United Kingdom
2 Current affiliation: Genomic Immunoepidemiology Division, HUMIGEN, Institute for Genetic Immunology, Hamilton, NJ 08690
3 Community Health and Epidemiology, Department of Paediatrics, Dalhousie University IWK Health Centre, Halifax, Nova Scotia B3K 6R8, Canada

DOI: 10.1093/aje/kwm158; Advance Access publication June 18, 2007